BPSU

British Paediatric Surveillance Unit

Annual Report 2020-2021

Surveillance of Rare Childhood Disease • BPSU •

Aims of the British Paediatric Surveillance Unit

To:

- Facilitate research into uncommon childhood infections and disorders for the advancement of knowledge and to effect practical improvement in prevention, treatment and service planning

- Allow paediatricians to participate in the surveillance of uncommon disorders and to lessen the burden on reporting doctors of such requests arising from numerous different sources

- Increase awareness within the medical profession of the less common disorders studied and respond rapidly to public health emergencies.

http://www.bpsu.org.uk

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Foreword


Prof Shamez Ladhani
Chair, BPSU

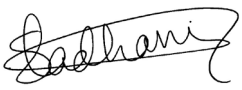
Where to start … my 3 years as the Chair of the BPSU has been a rollercoaster ride culminating in exciting new opportunities for the BPSU during the COVID-19 pandemic. The BPSU has been a world-leading national surveillance unit for rare diseases in children that is now being replicated in many countries worldwide. Forward planning with extensive scientific and administrative support has ensured that around a dozen studies are constantly underway across the UK and the Republic of Ireland.

My first experience with the BPSU was in 2001 when I was awarded the Sir Peter Tizard Bursary to conduct a study on imported malaria in children. Since then, I have had the privilege of being involved with numerous BPSU studies over the past two decades, which have contributed significantly to our knowledge of rare infectious diseases in children and helped inform national policy. The experiences I gained from BPSU studies alongside my role as the clinical lead for national surveillance of vaccine-preventable disease at Public Health England played an important part in shaping my vision for progressing the BPSU as the chairperson. One of the more significant steps forward was gaining an agreement by the BPSU scientific committee and governing board to fast-track surveillance studies identified as being of national importance. In the recent past, these would have included the global emergence of congenital Zika virus and a national outbreak of acute flaccid paralysis associated with enterovirus infections. It was this agreement that allowed rapid initiation of BPSU studies on PIMS-TS and neonatal COVID-19 during the current pandemic. We also proved the versatility of the BPSU by adapting a one-off survey to paediatricians on delayed presentations of children with severe and critical illness to hospital during the first national lockdown that was implemented in March 2020. The rapid responses by paediatricians helped change the “Stay at Home” message to emphasise the importance of seeking medical help if unwell.

Another important role of the BPSU that is often under-recognised is the commitment to education, hosting regular training sessions on rare childhood diseases, including online webinars during the pandemic. In April 2021, the BPSU also hosted a joint online symposium with Public Health England on COVID-19 from a paediatric perspective that received more than 2,000 registrations to attend from all parts of the world, the first of its kind to achieve such high participation rates. A recording of the symposium is available on our website: **BPSU-PHE Symposia series: COVID-19 from a Paediatric Perspective**

Finally, the BPSU team has worked really hard to facilitate the whole surveillance programme. We have worked with the RCPCH to facilitate external funding to support rare diseases surveillance, information dissemination and education. We are also working to develop a new online platform to facilitate both case reporting and questionnaire completion in near real-time, which is critical for new and emerging diseases, as we have learned from the pandemic. We hope that this new system will be up and running soon and will simplify processes for paediatricians and investigators.

It goes without saying that the success of the BPSU lies in the paediatricians across the UK and the Republic of Ireland who report cases and complete the detailed questionnaires sent to them by the study investigators. The BPSU methodology requires all paediatricians to complete a monthly e-card even if they have not seen any of the cases under surveillance. This is really important to ensure high case ascertainment for surveillance of rare diseases. I hope that paediatricians will continue to provide the same support for the BPSU and the new chairperson in the future. I would also like to take this opportunity to thank the BPSU scientific committee for all their support, encouragement and enthusiasm during my time as the chairperson of BPSU.



Shamez Ladhani. Chair BPSU,
October 2021

1 How the Surveillance System Works

Background

Rare diseases and infections are a numerically important cause of illness and death and mortality in childhood. There are upwards of 8,000 rare diseases and though individually uncommon, together they affect thousands. Many are characterised by chronicity, high rates of disability or death. These conditions pose a large financial and emotional burden for affected children, their families and health systems.

To address this problem in the UK and Ireland, the BPSU was set up in July 1986, enabling paediatricians to participate in the surveillance and further study of rare disorders affecting children.

Several agencies founded and continue collaborating to support the work of the BPSU: the Royal College of Paediatrics and Child Health (RCPCH), Public Health England (PHE), University College London GOS Institute of Child Health (UCL GOS ICH) and GOSH Children's Charity. The BPSU's Scientific Committee meets five or six times a year to consider individual applications and the progress of studies.

Selection of studies for inclusion in the scheme

Details on the selection process and application process for the BPSU is available at **http://www.rcpch.ac.uk/bpsu/apply**.

Each application requires approval from the BPSU Scientific committee, a Research Ethics Committee (REC), the Confidentiality Advisory Group (CAG) of the Health Research Authority and the Scottish Public Benefits and Privacy Panel (PBPP).

The reporting system

Surveillance is 'active' in that the BPSU office actively sends out each month an email to consultant paediatricians in the UK and Ireland. A link directs the recipient to the BPSU electronic-orange card ('eCard') - Figure 1); which is hosted securely on the UCL server. The eCard lists the conditions currently under surveillance. A set of instructions for completing the card, including case definitions of the conditions listed on the card is also circulated. When a new study begins, the mailing also includes a link to a specially produced study protocol card and other information about the study.

Participants are expected to return eCards **even if they have no cases to report** - there is a 'nothing to report' box for them to tick. This is an important feature of the surveillance scheme as it allows us to measure compliance, which is continually monitored, to the reporting system.

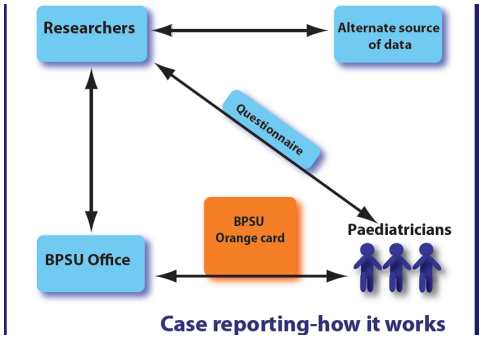
Figure 1: Orange eCard

Follow-up and confirmation of case reports

On receiving a case report the BPSU informs the relevant study team who send a short questionnaire to the reporting clinician to gather further information. Due to the need to discount duplicates a limited amount of patient identifiable data is collected. The study investigators report back to the BPSU, indicating when cases have been confirmed or are duplicate case reports (Figure 2). Duplication of reporting is most likely to occur when the condition requires referral to another clinician, but this is encouraged, as it is better to receive duplicate reports than to miss a case.

To improve case ascertainment for specific studies where a child may see specialist clinicians, consultants working in other specialties have been invited to participate in the scheme. Aside from helping to improve ascertainment, such complementary data sources help to validate the surveillance system.

Figure 2: Surveillance mechanism



2 Scientific Coodinator's Yearly Review of Activities

Six studies commenced surveillance in 2020, neonatal SARS-CoV-2 (COVID-19) – Dr Chris Gale, Imperial College; delayed presentations (one off survey) – Prof Shamez Ladhani, PHE; paediatric multisystem inflammatory syndrome (PMIS) – Prof Shamez Ladhani, PHE; conservative care in end-stage kidney disease – Dr Lucy Plumb, Southmead Hospital;; glucocorticoid induced adrenal suppression – Dr Tim Cheetham ,Royal The Great North Children's Hospital; and chronic recurrent multifocal osteomyelitis/ chronic nonbacterial osteomyelitis (CRMO/CNO) – Dr Chenqu Suo Addenbrookes hospital.

Four studies had their period of surveillance extended: pneumococcal meningitis, herpes simplex virus, congenital rubella, progressive intellectual and neurological deterioration.

Severe chronic fatigue, food protein-induced enterocolitis syndrome, Sydenham chorea and congenital ichthyosis ended surveillance in 2020.

During 2020-21, there were 15 publications relating to BPSU studies (see Appendices, p.24).

Participation in the scheme during the year 2020

The overall card return compliance rate for the year 2020, calculated as a proportion of orange cards returned, was 88.30% (43,514/49,236) a fall of 2.5% from 2019. Monthly response rates ranged from 91.9% in February to 82.3% in December with a median of 88.6%. Details of regional response rates are provided in Table 1 overleaf. The rate has again fallen and action is being taken to address this fall. Of concern is the increased in those for whom no case report was received over the year. We are making an even greater effort to raise awareness of the activity amongst trainees and are identifying regional champions to promote the activity.

Table 2 summarises the outcome of the follow-up of cases and provides evidence for their level of accuracy of reporting by clinician. By the end of a study 80-95% of the questionnaires will have been returned. The time taken to follow-up varies between conditions and may be longer if microbiological/pathological details are required; or if a specialist committee has to convene to adjudicate on the case data.

Workload of those reporting in the scheme: 979 of 4,277 (22.9%) receiving an eCard reported a case in 2020. 602 (14.1%) reported a single case, 308 (7.2%) reported between two and four cases and 69 (1.6%) reported five or more cases. The greatest number of cases reported by an individual was 69 cases.

Public and patient engagement

The BPSU remains committed to wider public patient engagement (PPE) in the development and dissemination of our work and that of the studies. To support clinicians when preparing their protocols several resource packs have been introduced. These are available at **http://www.rcpch.ac.uk/bpsu/apply**.

Unfortunately, the 2020 tea party had to be cancelled due to the COVID-19 pandemic. The tea party brings representatives from across the rare disease community to hear the experiences of children young people living with rare disease and the latest research in the field.

The BPSU continues to contribute to work of patient advocacy groups such as Rare Disease UK, Cambridge Rare Disease Network, Rare Revolution Magazine and Findacure. The BPSU also works with Medics 4 Rare Diseases helping to raise awareness of rare disease research amongst student medics and trainees.

Education

With the RCPCH the BPSU organises a rare disease webinar series; this year we've produced webinars on nutritional rickets, type-2 diabetes (**http://rcpch.ac.uk/bpsu/t2d**) and Behçet's syndrome (**https://www.rcpch.ac.uk/work-we-do/bpsu/study-behcets-syndrome**).

International activities

The BPSU continues to take an important role in the activities of the International Network of Paediatric Surveillance Units (INoPSU). The BPSU developed a searchable database of over 200 rare paediatric conditions surveyed by units within INoPSU (**http://www.inopsu.com**). Here you will also find information on affiliated national surveillance units, studies currently being undertaken; published papers; study protocols; and questionnaires.

Funding

BPSU is funded through grants from UCL GOS Institute of Child Health, Great Ormond Street Hospital Children's Charity, RCPCH, and Public Health England along with contributions from researchers.

Table 1: Regional Response rate 2020 and 2019

Region	% return	Rank 2020	Rank 2019
East Anglia	90.0%	7	8
Mersey	87.0%	16	15
NET	83.3%	19	20
North Scotland	93.6%	1	2
North Western	87.4%	15	16
Northern	93.1%	3	5
Northern Ireland	90.2%	5	6
NWT	87.6%	14	3
Oxford	87.7%	13	18
Republic of Ireland	82.1%	20	19
SET	84.6%	18	17
South Scotland	85.6%	17	12
South Western	90.2%	6	9
SWT	89.2%	10	10
Trent	88.4%	12	14
Wales	92.9%	4	1
Wessex	89.7%	8	13
West Midlands	89.6%	9	7
West Scotland	88.7%	11	11
Yorkshire	93.3%	2	4

Figure 3: Regional Response rate 2020

Table 2: Outcome of follow-up of the cases reported in 2020 for conditions under surveillance

Condition under surveillance	Date when reporting began	Valid reports	%	Duplicates	Errors	(D&E) %	Not yet known	%	Total
CRU	Jun-91	93	45	42	67	52	6	3	208
PIND	May-97	2,505	51	607	1,277	39	489	10	4,406
ICH	Nov-18	28	29	31	34	66	5	5	98
SC	Nov-18	40	52	9	6	19	22	29	77
FPIES	Jan-19	98	47	7	78	41	26	12	209
CFS	Feb-19	131	46	2	23	9	126	45	282
HSV	Jul-19	76	39	34	9	22	75	39	194
PNE	Jan-20	45	42	10	7	16	44	42	106
COV	Mar-20	549	54	116	193	30	160	16	1018
PMIS	Mar-20	748	49	192	89	18	508	33	1537
ASU	Sep-20	7	7	0	27	28	61	64	95
ESK	Sep-20	18	21	1	3	5	62	74	84
CNO	Oct-20	42	36	6	18	21	51	44	117
RES	Nov-20	29	36	2	15	21	35	43	81
Total		**4,409**	**49**	**1,059**	**1,846**	**32**	**1,670**	**19**	**8,984**

CRU Congenital rubella
PIND Progressive intellectual and neurological deterioration
ICH Ichthyosis
SC Sydenham's chorea
FPIES Food protein induced enterocolitis syndrome
CFS Severe chronic fatigue syndrome
HSV Neonatal herpes simplex virus
PNE Clinical charateristics of pneumococcal meningitis
COV Neonatal complications of coronavirus disease (COVID-19)
PMIS Paediatric multisystem inflammatory syndrome, Kawasaki disease and toxic shock syndrome
ASU Glucocorticoid induced adrenal suppression
ESK Conservative care in end-stage kidney disease
CNO Chronic recurrent multifocal osteomyelitis/ chronic nonbacterial osteomyelitis
RES Outcome of resuscitated term babies with no heart rate detected at 10 minutes of age

3 Surveillance Studies Undertaken in 2020

Once again individual reports have concentrated on the summary of the condition and on the analysis. General methodology information is contained in the study protocols and can be found at https://www.bpsu.org.uk. The analysis presented here is provisional and has yet to be peer reviewed.

The investigators would like to acknowledge all those who are involved in their projects but are not mentioned. The BPSU would like to thank all those paediatricians who have returned cards, reported cases and completed the questionnaires.

Congenital rubella

Key points

- Between April 2020 and March 2021 there have been no reports of CR to the BPSU.
- Since 2005 13 congenital rubella births were reported in the UK.
- Antenatal screening for rubella susceptibility was discontinued in England in April 2016.
- Rubella is a notifiable disease and is monitored by Public Health England.

Summary

Rubella has been a notifiable disease[1] since 1988 and is monitored by Public Health England (PHE) rubella surveillance programme team, part of the National Infection Service based at PHE Colindale. In addition, the Integrated Screening Outcomes Surveillance Service (ISOSS), part of Public Health England's Infectious Diseases in Pregnancy Screening (IDPS) Programme,[2] maintains national surveillance of congenital rubella (CR) cases in the UK. This remains important following the discontinuation of screening for rubella susceptibility in pregnant women in England in April 2016.[3]

The IDPS programme commission the BPSU to provide case notifications on CR in England to the ISOSS team based at UCL's Great Ormond Street Institute of Child Health.

Surveillance period

January 1990 and is reviewed yearly.

Methodology

The team liaise with the IDPS programme and the rubella surveillance team on any notifications. Case data are then collected directly from paediatricians by the ISOSS team. ISOSS collects patient data under legal permissions granted to PHE under regulation 3 of the Health Service (Control of Patient Information) Regulations 2002. The ISOSS team then conduct enhanced data collection on any confirmed case to review with the IDPS and NIS team to ascertain contributory factors and inform and evidence any potential policy or programme reviews.

Details of the protocol are available at **http://www.rcpch.ac.uk/bpsu/congenitalrubella**

ISOSS team

Analysis

Between April 2020 and March 2021 there have been no reports of CR to the BPSU.

Since 2005 there have been 13 confirmed reports of CR (Table 3). None of the mothers was UK-born, and none had a previous pregnancy in the UK. Seven of the women acquired their infection abroad in early pregnancy and six were exposed to rubella in the UK.

Table 3: Confirmed and compatible congenital rubella births in the UK and Ireland 2005 to March 2021

	Primary Source of notification		
Year of birth	**BPSU**	**Other**	**Total**
2005-09 *	4	2	6
2010-21 *	6	1	7
Total	**10**	**3**	**15**

*** includes a stillborn infant**
^ includes a set of triplets, one of whom was stillborn

Discussion

Very few cases of CR have been reported in the last decade, with none since 2018. Most reports concern infants with neonatal symptoms who also had serious rubella-associated defects identified at birth or soon afterwards. In the last 15 years, only half of the maternal infections were acquired in the UK. Pregnant women may enter the UK having acquired infection in early pregnancy elsewhere, and susceptible women resident in the UK who travel abroad during early pregnancy may also come into contact with rubella.

All health professionals, particularly paediatricians, those working in primary care and antenatal care, or with refugees or other recent migrants, must continue to be aware of the potential serious implications of rash or rash illness in

early pregnancy. Updated PHE guidelines for the management of viral rash in pregnancy and a quick reference guide are available at **https://www.gov.uk/government/publications/viral-rash-in-pregnancy**

Since cessation of rubella susceptibility screening in pregnancy in 2016 there have been no cases of congenital rubella reported where the mother acquired rubella in the UK. To achieve continued population level control of rubella, the key action is still MMR vaccination. The measles and rubella elimination UK strategy 2019 (**https://www.gov.uk/government/publications/measles-and-rubella-elimination-uk-strategy**) focuses on four core components required to maintain elimination of measles and rubella:

1. Achieve and sustain ≥ 95% coverage in the routine childhood programme.
2. Achieve ≥ 95% coverage with 2 doses of MMR vaccine in older age cohorts through opportunistic and targeted catch-up.
3. Strengthen measles and rubella surveillance.
4. Ensure easy access to high-quality, evidence-based information

Integrated Screening Outcomes Surveillance Service

ISOSS is part of Public Health England's IDPS programme.ISOSS is commissioned to conduct surveillance of the three infections screened for in pregnancy: HIV, syphilis and hepatitis B, as well as to monitor any cases of congenital rubella (**https://www.ucl.ac.uk/isoss**).

HIV surveillance: All pregnancies to women living with HIV, their infants and any children diagnosed with HIV (<16 years) are reported to ISOSS using a bespoke secure online portal. This data has been collected for over 30 years and provides a unique comprehensive population-level surveillance that informs national guidelines and policy, as well as supporting collaborations more widely.

Currently nearly 90% of women living with HIV who become pregnant are already aware of their status, the majority of women deliver with undetectable viral load and the current vertical transmission rate stands at under 0.3%. ISOSS also conducts an enhanced data collection of all HIV vertical transmissions in UK-born children; all cases are included in a national review by an Clinical Expert Review Panel (CERP). The findings are fed back to the IDPS Programme to evidence and inform future service provision: **https://www.gov.uk/government/publications/integrated-screening-outcomes-surveillance-service-isoss-annual-report/integrated-screening-outcomes-surveillance-service-isoss-annual-report-2021**

Syphilis surveillance

Active surveillance of congenital syphilis in the UK by the ISOSS Team commenced in 2019. All cases of congenital syphilis (confirmed or suspected) born in the UK are reported to ISOSS and will be included in a review by a CERP in order to inform national guidelines and policy (**https://www.ucl.ac.uk/integrated-screening-outcomes-surveillance/about-isoss/phes-infectious-diseases-pregnancy-screening-idps-clinical-expert-review-panels**). Surveillance of all women who screen positive for syphillis in pregnancy was launched in 2020. From mid-2020 data collection of infants born to syphilis screen positive mothers who required treatment in pregnancy began. Data collection forms are designed to support the British Association for Sexual Health and HIV (BASHH) Syphilis Birth Plan (**https://www.bashhguidelines.org/media/1196/syphillis-bp_print_2016_p3.pdf**).

ISOSS completed a retrospective review of infants diagnosed with congenital syphilis between 2015 and 2020 (reported by June 2020). A report summarising the findings on the 24 reported infants has been produced by the IDPS programme **https://www.gov.uk/government/publications/integrated-screening-outcomes-surveillance-service-isoss-annual-report/isoss-congenital-syphilis-case-review-report-2015-to-2020**.

Hepatitis B Surveillance

Surveillance of all women who screen positive for hepatitis B in pregnancy launched in mid-2021 for women booking for antenatal care and/or women who screen positive from 01/04/2021. The ISOSS team will commence surveillance of infants exposed to hepatitis B in pregnancy and children with hepatitis B born to this cohort of women onwards - **https://www.gov.uk/government/publications/integrated-screening-outcomes-surveillance-service-isoss-annual-report/integrated-screening-outcomes-surveillance-service-isoss-annual-report-2021**. ISOSS and the IDPS programme team work closely with the Immunisations and Countermeasures team at the National Infection Service, in the delivery of the enhanced hepatitis B pathways and in monitoring hepatitis B exposed and any children diagnosed with hepatitis B. Outcome information will be sought on all hepatitis B exposed infants via the dry blood spot testing service provided by Colindale, and via reporting of serology testing of infants.

References

1. **https://www.gov.uk/guidance/notifiablediseases-and-causative-organisms-how-toreport**

2.**https://www.gov.uk/guidance/infectious-diseases-in-pregnancy-screening-programme-overview**

3. **https://phescreening.blog.gov.uk/2016/03/31/rubella-susceptibility-screening-in-pregnancy-ends-tomorrow/**

4. **https://www.gov.uk/government/collections/immunisation**

5. **https://www.gov.uk/government/publications/integrated-screening-outcomes-surveillance-service-isoss**

Funding

Public Health England's Infectious Diseases in Pregnancy Screening (IDPS).

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Neonatal complications of coronavirus disease (COVID-19)

Dr Chris Gale

Key points

- 685 cases in total notified since study start; notifications have now fallen considerably.
- 60% (126/209) notified cases relate to neonates with SARS-CoV-2 infection admitted to hospital.
- 40% (83/209) of cases relate to mothers with confirmed COVID-19 infection; from 1 April 2021 only cases relating to neonates with COVID-19 reported.

Summary

The virus SARS-CoV-2 is circulating worldwide and it is important to investigate how babies can catch it, whether this can happen in pregnancy before they are born, during labour, or after birth, how sick they are when infected, and what happens to babies when their mother gets COVID-19 in pregnancy. This study is a national project collecting information about newborn babies who have COVID-19 and need hospital care or whose mother had COVID-19 at the time of their birth. Doctors in the UK report any babies that meet one of these definitions to the BPSU on a regular basis. When a case is reported, the study team ask the doctor to fill out a form giving information about the baby, their birth, their symptoms, and any COVID-19 tests they or their mother have had. The study team regularly analyse the information to describe how many infected newborn babies there are, their characteristics including how sick they are and when and how COVID-19 may have been transmitted to them. Regular reports, initially weekly and now fortnightly, are sent to the Departments of Health in the four UK nations and the relevant Royal Colleges. The information is used to inform the national COVID-19 response and to support the development of guidelines for professionals caring for pregnant women and newborn babies, and provide information for pregnant women and parents.

Surveillance period

April 2020 - September 2021 (inclusive)

Follow-up period: For a six-month period ending in March 2022.

Methodology

From 01 April 2020 to 31 March 2021, weekly reports of cases were requested (rather than monthly) due to this being an urgent public health study; this moved back to monthly which will continue until September 2021. Details of the protocol are available at **http://www.rcpch.ac.uk/bpsu/covid19**

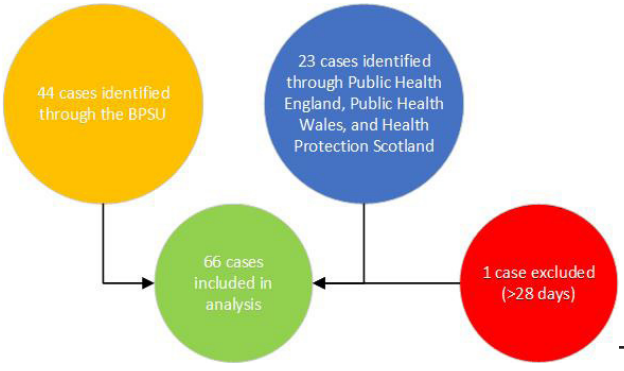
From 1 April 2021 the case definition was changed removing the requirement to report neonates who had been exposed to COVID-19 at the time of birth and admitted for neonatal care.

Analysis

We analysed the initial data (March to April 2020) relating to the neonates infected with SARs-CoV-2 (category 1 case definition) and these data have been published in the Lancet Child and Adolescent Health.[1,2] Analysis of the data relating to neonates born to mothers with COVID-19 and admitted for neonatal intensive care (category 2 case definition) is currently underway. The findings relating to the former are summarised here:

Using the BPSU we carried out a prospective UK population-based cohort study of babies with confirmed SARS-CoV-2 infection in the first 28 days after birth who received inpatient care. Active national surveillance via the BPSU was used to identify infected babies with case identification supplemented by linkage to: national testing data from Public Health England and Public Health Scotland, the national Paediatric Intensive Care Audit Network (PICANet), the MBRRACE-UK surveillance of perinatal deaths, and the concurrent UKOSS obstetric surveillance study of COVID-19 in pregnancy. The first data analysis reported included eligible babies who were inpatients between March 1 and

Figure 4: All Cases reported by BPSU and public health agencies



April 30, 2020.[1,2] Outcomes reported included the incidence (per 10,000 livebirths) of confirmed SARS-CoV-2 infection and severe disease, the proportions of babies with suspected vertically (likely to have been acquired from their mother) and nosocomially (suspected to have been acquired from the hospital) acquired infection, their clinical characteristics and outcomes.

During this period 66 babies with confirmed SARS-CoV-2 infection were identified representing an incidence of 5·6 per 10,000 livebirths (95% CI 4·3–7·1). Of these babies 28 (42%) had severe neonatal SARS-CoV-2 infection giving an incidence of 2·4 per 10,000 livebirths (95%CI 1·6–3·4); 16 (24%) were born preterm.

The incidence of SARS CoV2 infection was analysed by ethnic group; overall 36 (55%) babies were from white ethnic groups (incidence 4·6 per 10,000 livebirths of white babies (95%CI 3·2–6·4)); 14 (21%) were from Asian ethnic groups (incidence 15·2 per 10,000 livebirths of Asian babies (95%CI 8·3–25·5)); eight (12%) were from Black ethnic groups (incidence 18·0 per 10,000 livebirths of Black babies (95% CI 7·8–35·5)); and seven (11%) were from mixed or other ethnicities (incidence 5·6 per 10,000 livebirths from mixed or other ethnic group babies (95% CI 2·2–11·5)). 17 (26%) babies with confirmed infection were born to mothers with known perinatal SARS-CoV-2 infection, and two (3%) were considered to have possible vertically acquired infection defined as a SARS-CoV-2-positive sample within 12 hrs of birth where the mother was also positive. Whereas eight (12%) babies had suspected nosocomially acquired infection. As of July 28, 2020, when this analysis was conducted, one baby (2%) had died of a cause unrelated to SARS-CoV-2 infection.

Discussion

We concluded that during the height of the first wave of SARS-CoV-2 infection in the UK neonatal SARS-CoV-2 infection was uncommon in babies admitted to hospital. Infection with neonatal admission following birth to a mother with perinatal COVID-19 also appeared uncommon, and possible vertical transmission was rare. This supported the international guidance issued at that time and still extant to avoid separation of mother and baby. The high proportion of babies from Black, Asian, or minority ethnic groups reflected the findings from the UKOSS study of COVID-19 in pregnancy and the rates of infection in the general population; further investigation of this disparity is required.

References

1. Gale C, Quigley MA, Placzek A, Knight M, Ladhani S, Draper ES, Sharkey D, Doherty C, Mactier H, Kurinczuk JJ. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. Lancet Child Adolesc Health. 2021; 5: 113–21. On-line: 2020 Nov 9:S2352-4642(20)30342-4. doi: 10.1016/S2352-4642(20)30342-4

2. Gale C, Quigley MA, Placzek A, Knight M, Ladhani S, Draper ES, Sharkey D, Doherty C, Mactier H, Kurinczuk JJ. The ability of the neonatal immune response to handle SARS-CoV-2 infection – Authors' reply. Lancet Child Adolesc Health. 2021 Mar;5(3):e8.

Public and patient engagement

Bliss
Web: **https://bliss.org.uk**

Sand: Stillbirth and neonatal death charity
Web: **https://sands.org.uk**

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Herpes simplex virus in neonates

Key points

- 166 case notifications have been reported with 80 confirmed cases with an estimated incidence is 5.2 cases/100-000 live births so far, based on 2019 and 2020 UK live births (likely to be an underestimate due to 45 pending responses).
- 3.8% were born prematurely, less than 37 weeks. 26.9% of cases had disseminated disease, of whom 52.3% were premature. Overall mortality was 23.1% but from disseminated disease it was 71.4%.
- Presenting features of disseminated disease were non-specific; only 23.8% presented with fever and only 38.1% presented with skin, eye or mouth lesions.

Summary

Neonatal herpes simplex virus (HSV) disease is a potentially devastating condition which can lead to significant morbidity and death.[1] Transmission typically occurs during delivery through an infected birth canal, or after delivery, following exposure to HSV infections such as cold sores.

Sexually transmitted herpes infections in adults increased in the last decade and we suspect that the number of cases of neonatal HSV is therefore also rising. The incidence increased from 1.65 to 3.58 / 100 000 live births between the first national BPSU study (1986-1991) and the second (2004-2006).[2] A recent local study from Nottingham[3] showed rates of 17.5 / 100 000 live births, ten times higher than the first BPSU study and an overall mortality rate of 47%.

We currently do not have enough information about national incidence, which babies are most at risk, ways we might be able to reduce those risks and whether the treatment and prophylaxis we are using is reducing long term problems and later relapses. There is a lack of clarity as to the optimum management of mothers and babies who are at risk: a number of different guidelines are available for clinicians to follow, resulting in variation in practice across sites.

This is of specific relevance to neonates presenting to the emergency department with non-specific signs of sepsis. Currently not all babies are treated for HSV; however, if the prevalence of HSV has increased significantly nationwide to those approaching levels in Nottingham, this may need to be considered.

Surveillance period

July 2021 - January 2022 (inclusive).

Follow-up period: For a twelve-month period ending in January 2023.

Dr Katy Fidler

Methodology

Data capture uses standard BPSU methodology. Details of the study protocol are available at **http://www.rcpch.ac.uk/bpsu/hsv**

Analysis

This is an interim analysis based on data collected during the first 22-months of the surveillance period. A more detailed analysis will be conducted on completion of the study.

Between July 2019 and April 2021 (inclusive), we received 166 case notifications with 80 confirmed cases of neonatal HSV infection (remaining notifications included 9 reporting errors, 47 pending responses and 30 confirmed duplicates).

Of the confirmed cases 4/80 (42.5%) infants were female; 46/80 (57.5%) were male. 35/78 (44.9%) had HSV-1 and 40/78 (51.3%) had HSV-2; 3/78 (3.8%) cases suspected/virus type not reported. 11/77 (14.3%) were very or extremely premature (<32 weeks), 15/77 (19.5%) were moderate to late premature (32 to 36+6 weeks) and 51/77 (66.2%) were term. The average age of the mother was 26.7 years, which was younger than the average age of the UK mother at delivery in 2019 (30.7 years).

The mother was reported as the source of infection in 27/78 (34.6%) of cases. 14/27 (51.9%) maternal sources of infection had genital infection, 5/27 (18.5%) had mouth/skin lesions, 1/27 (3.7%) had 'systemic HSV without genital lesions' and no site was reported for the remaining seven cases.

Cases were classified into disseminated (widespread, multi-organ involvement), meningoencephalitis (involvement of CNS), viraemia (not disseminated) and SEM (localized skin/eye/mouth lesions). 21/78 (26.9%) had disseminated disease, of whom 11/21 (52.3%) were born premature. 29/78 (37.1%) had meningoencephalitis, 13/78 (16.7%) had viraemia and 15/78 (19.2%) had SEM.

In disseminated disease, presenting features were non-specific: only five (23.8%) presented with fever and eight (38.1%) presented with skin/eye/mouth lesions. 17 (80.9%) of infants with disseminated disease presented with "sepsis". Mean admission CRP for disseminated disease: 27 mg/L, viraemic

disease 3.9mg/L, CNS 10.1mg/L, SEM 7.1 mg/L. Admission ALT was significantly higher in disseminated disease compared to other groups.

Aciclovir was given in 75/78 (96.2%) of cases, but only started on day of presentation in 32/78 cases (41.0%). There was a treatment delay of ≥2 days from day of presentation in 23/78 (29.5%) cases. Overall mortality was 23.1% (18/78 cases). 12/18 (66.7%) had HSV2. 9/26 (34.6%) of premature infants died. 9/51 (17.6%) of term infants died. 15/21 (71.4%) of cases with disseminated disease died including all three (20%) who did not receive aciclovir.

Discussion

Analysis of preliminary data demonstrates an increased incidence of neonatal herpes simplex virus disease compared to findings of the previous BPSU studies. Incidence is estimated using incomplete data, and is likely to increase further once the remaining questionnaires are included in calculations. Incidence seems to have decreased during the COVID pandemic. Prognosis for infants with disseminated infection remains poor, even in those receiving antiviral treatment.

These results remind us of the challenges of detecting disseminated HSV infection in unwell infants. Typical makers of serious infection such as fever and abnormalities in CRP at presentation are absent from the majority of cases. Characteristic skin lesions are also not consistently present at the onset of illness. Dr Katy Fidler and Dr Julia Dudley have made educational films alongside this study to improve healthcare professional and public awareness of this infectious disease.

A full discussion will take place once data collection is complete. We note that service disruptions caused by the COVID pandemic may have caused reductions or delays in clinician case reporting. Analysis of monthly incidence will also be completed at the end of the surveillance period and the COVID period compared to non-COVID period to determine if social distancing measures could have influenced postnatal acquisition of this virus or indeed primary genital HSV in pregnancy. The results of this study will also inform work on national guidance on when to start aciclovir treatment in unwell neonates presenting to the emergency department or neonatal unit.

Public and patient engagement

The Herpes Viruses Association
Web: **https://www.herpes.org.uk**

Kit Tarka Foundation
Web: **https://www.kittarkafoundation.org**

Funding

This study is funded by the Rockinghorse Children's Charity and by the Kit Tarka Foundation.

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Ichthyosis in neonates

Key points

- By the end of the two year surveillance of new births, we had identified zero cases of harlequin ichthyosis and 29 cases of collodion membrane; of the latter, 26 had non-syndromic autosomal recessive congenital ichthyosis (ARCI) and three had syndromic ichthyosis.
- To optimise capture of new births including still-births we set up a collaboration with the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). Data are available for the first six months in which they identified five possible additional cases which are still being checked for eligibility.
- 12-month follow-up will be completed on 31 October 2021: to date one baby with ARCI and one with syndromic ichthyosis have died

Summary

Ichthyosis is a group of incurable genetic conditions with abnormally thick, scaly skin. The severe types, collodion membrane (CM) and harlequin ichthyosis (HI), are present at birth and can cause significant problems. Some babies do not survive, most deaths occurring at or within days of birth. HI and CM are very rare. There is no proven correct treatment, so practice varies, for example some babies remain in the neonatal intensive care unit for weeks whilst others are nursed on a ward.

Compared with other rare diseases (for example the skin-fragility disorder epidermolysis bullosa) there is no national specialised service for ichthyosis, even though the morbidity and mortality are similar. Families often rely on each other for advice, for example via the Ichthyosis Support Group (ISG).

Our study aimed to estimate the number of new cases per year in the UK and Ireland, death rate and illness within the first year of life.

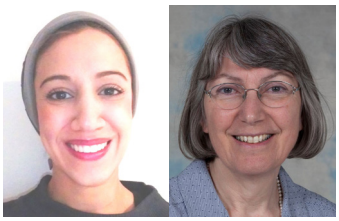
At the time of this report some gaps remain in our data but we can state that during the study period no babies were born with HI and 29 were born with CM, of whom two died within 14-weeks of birth.

Information will be made available to medical professionals and to parents via the ISG, with the aim to improve the care of babies with ichthyosis. Our data will also be used to support an application to NHS England for a Highly Specialised Service for ichthyosis.

Surveillance period

November 2018 - November 2020 (inclusive).

Follow-up period: For a twelve-month period until November 2021.



Dr Fozia Roked & Professor Celia Moss

Methodology

Data capture uses standard BPSU methodology. Details of the study protocol are available at **http://www.rcpch.ac.uk/bpsu/ichthyosis**

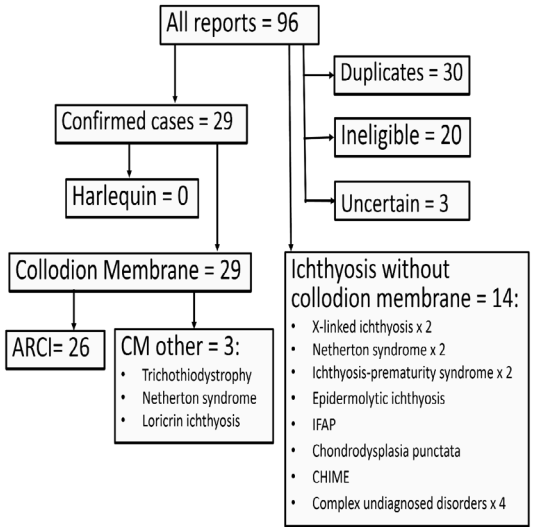
Some cases may not be reported if they have not been seen by a paediatrician after birth e.g. those who are still born or die immediately after birth. Therefore, data will be cross checked with National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) once appropriate approvals are received.

Analysis

Ninety-six cases were notified to BPSU, and we eventually obtained information on all of these. Of the 96 case reports, 30 proved to be duplicates, and 20 were ineligible, mostly because they had been born before the study period (Figure 5). Some cases did not match the case definition (harlequin or collodion) but did have congenital ichthyosis. It was difficult to be certain about the status of these cases because we were not able to request photographs without patient consent, so we often asked the local dermatologists to help clarify this. Three remain uncertain pending further information.

We received 14 reports of babies with ichthyosis but without the clinical appearance of harlequin or collodion membrane. In most cases, the reporter initially diagnosed collodion membrane but this was not confirmed by the local dermatologist. As far as we can establish none of these had autosomal recessive congenital ichthyosis (ARCI).

Figure 5: Breakdown of case reports



In addition, we are awaiting information on five cases identified by NCARDRS and born during the first six-months of our surveillance period, as well as cases identified by NCARDRS during the latter 18-months of our study which have not yet been shared with us, Of the first five NCARDRS cases, one is confirmed, two are ineligible and two have not yet replied. This interim analysis is based on the 29 so-far confirmed cases identified via BPSU.

Our interim incidence estimates (mean and 95% confidence intervals) based on the 2019 figure of 772,476 live births in the UK and Ireland is, for CM,1.877 per 100,000 live births, for UK and Ireland (95% confidence interval 1.871 – 1.883). There were no cases of HI during the study period although we are aware of two cases in the six-months before and one case soon after.

CM is not a precise diagnosis, but a descriptive term of a neonatal appearance that can evolve into several different types of ichthyosis. Of the 29 cases, three proved to have syndromic ichthyosis, with other complicating co-morbidities which were identified in the neonatal period. We excluded these three cases from further analysis of outcomes leaving a more homogeneous group of 26 that fitted the diagnosis of non-syndromic ARCI. ARCI is the major cause of CM.

Our study may underestimate the incidence of ARCI because some patients with ARCI have no history of CM at birth. The study was designed specifically to look at neonatal management of CM.

Of 26 with ARCI, just over half (53.9%) were male infants; 24 (92.3%) had no family history of ichthyosis. Parental consanguinity was reported in one case; ethnicity was White in 15, South Asian in six, African-Caribbean in two and mixed in three. Median (range) values for birth parameters were: gestation 37^{6} (35^{4}–40^{1}) $weeks^{days}$, birth weight 3.0 (2.2–4.1) Kg; Apgar score at ten minutes 10 (7–10). Of 26 ARCI cases, 21 (80%) were nursed in an incubator; two (7.7%) were intubated – one for hernia surgery and one with preterminal sepsis; 16 received intravenous antibiotics (61.5%); one was treated with acitretin. Median age at discharge was 11 (2–30) days. In at least four cases the ichthyosis resolved within a month. Comorbidities included one case each of diaphragmatic hernia, undescended testes and trisomy. Twenty-five of the 26 are alive to date except one who died aged eight-days with hospital-acquired infection; 15 have reached their first birthday (survival 93% at 12-months).

Of the three CM babies who did not have ARCI, one had an unusual autosomal dominant non-syndromic ichthyosis diagnosed on family history; one had Netherton syndrome and one had trichothiodystrophy with severe cardiac anomalies and died at age 14-weeks.

Discussion

This study is the first to estimate incidence of collodion membrane and harlequin ichthyosis in the UK and Ireland. Our prior incidence estimate for CM (13 per year) proved remarkably accurate (29 over 2 years). However, we were surprised to find not a single case of HI (prediction 3-4 per year). We have questioned dermatologists around the country none of whom know of a case and we believe this means that indeed none occurred. We are aware of two babies with HI born within the six-month period before the start of the surveillance period (both of whom survived) and have been notified of a baby born seven-weeks after the end who died at nine-days.

The ICD10 coding for ichthyosis is problematic. CM Q80.2 is a description not a diagnosis: it is a neonatal appearance that can evolve into several different genetic conditions. We used this term because CM is a clearly identifiable appearance and because our aim was to find out how neonatologists manage this condition at birth. However, this limits the usefulness of our incidence data as it does not tell us the incidence of a specific disease. Most CM (26/29; 90%) evolves into ARCI but this still does not give us an incidence for ARCI because, rarely, ARCI develops with no history of CM.

The three non-ARCI babies were easily identified at birth. One had a clear autosomal dominant family history (of loricrin ichthyosis). The baby with trichothiodystrophy had additional congenital anomalies and the diagnosis was made soon after birth. The baby with Netherton syndrome had a mild CM with other skin and hair features leading to an early diagnosis. Therefore it seems that otherwise apparently healthy babies born with a typical collodion membrane and family history consistent with recessive inheritance are likely to have non-syndromic ARCI.

Interim analysis was carried out on the 26 babies with CM and ARCI as this was a relatively homogeneous group. We confirmed a relatively early gestational age (median 37^{6}) which is already known for ARCI. We were pleased to find that most babies were seen early on by a dermatologist, and where necessary by an ophthalmologist. Although there was uncertainty among paediatricians about the diagnosis (some reported HI when the history and description clearly indicated CM) only one was given acitretin, a treatment generally reserved for those with HI, at least in the neonatal period. Most received intravenous antibiotics which we suspect were in many cases unnecessary but an understandable response of paediatricians to a baby with cracks in their skin. However we noted that in most cases interventions were conservative and babies were usually discharged early.

We do not yet have complete 12-month survival data but so far we are aware of two deaths which is lower than published rates.

Public and patient engagement

Ichthyosis Support Group
Web: **https://www.ichthyosis.org.uk**

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Funding

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Multisystem inflammatory syndrome, Kawasaki disease and toxic shock syndrome

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Key points

- There were 216 cases with features of Paediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) alone, 13 with features of both PIMS-TS and Kawasaki disease (KD), 28 with features of PIMS-TS and toxic shock syndrome (TSS) and 11 with features of PIMS-TS, KD and TSS, with differences in age, ethnicity, clinical presentation and disease severity between the phenotypic groups.
- There was a strong geographical and temporal association between SARS-CoV-2 infection rates and PIMS-TS cases.
- The strong association between SARS-CoV-2 infection and PIMS-TS emphasises the importance of maintaining low community infection rates to reduce the risk of this rare but severe complication in children and adolescents.

Summary

Coronavirus disease (COVID-19), is caused by a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The infection has spread rapidly across the globe with more than three million cases and over 200,000 deaths reported worldwide at the time of writing. The virus is transmitted through respiratory droplets and direct contact and usually causes a respiratory illness. Common symptoms include fever and dry cough. Children appear to be at lower risk of COVID-19, being responsible for around 1% of cases. Unlike adults, they usually have a very mild illness and it is rarely fatal. Recently, however, a number of children across the United Kingdom (UK) and in other part of the world have been reported to have a severe illness, often requiring admission to a paediatric intensive care unit because they are so unwell. Many children had symptoms common to both Kawasaki disease, which causes inflammation of the arteries, and Toxic Shock syndrome, a rare life-threatening immune reaction to certain infections.

Although such cases are rare, at present, we don't understand the relationship between SARS-CoV-2 and multi-system hyperinflammation in children. We want to find out how common this condition is across the UK and Ireland, what the common symptoms are and whether they are related to SARS-CoV-2.

Surveillance period

March 2020 - March 2022 (inclusive).
Follow-up period: Follow-up questionnaire at 12 months ending in March 2023.

Methodology

Data capture uses standard BPSU methodology. Details of the study protocol are available at **https://www.rcpch.ac.uk/bpsu/multisystem-inflammatory-syndrome**

Analysis

Data collection is still ongoing and final analysis will be conducted at the end of the surveillance period, including the incidence. In addition, BPSU is the only reporting source. Preliminary analysis relating to cases with symptom onset between 01 March and 15 June 2020 were included in this analysis outlined below.

There were 449 cases reported to BPSU. Eighty-nine duplicates were removed, 12 were >16 years old and five had onset dates pre 01 March 2020. This left 343 cases with illness onset between 01 March and 15 June 2020; 268 were classified as PIMS-TS and included in the analysis. The remaining 75 cases included 56 cases that did not fulfil the PIMS-TS, KD or TSS criteria (35 because of C-reactive protein (CRP) <100 mg/L, eight because CRP level was missing; 13 lacked other criteria), 13 with KD only, two with TSS only and four with KD/TSS.

Of the PIMS-TS cases, 246 were in England, six in Scotland, 11 in Wales, two in Northern Ireland, and three in the Republic of Ireland.

Cases were categorised based on pre-defined syndromic criteria and included 216 cases classified as PIMS-TS only without features of KD or TSS, 13 with PIMS-TS and complete/typical KD (PIMS-TS/KD), 28 cases with PIMS-TS and TSS (PIMS-TS/TSS) and 11 with all three phenotypes (PIMS-TS/KD/TSS). Three children died (all male), accounting for 3.6% (1/ 28) with PIMS-TS/TSS and 0.9% (2/216) with PIMS-TS only.

Discussion

Enhanced prospective national surveillance identified 268 cases that fulfilled a broad case definition for PIMS-TS since the start of the COVID-19 pandemic in the UK and Ireland. Cases differed in age, ethnicity, clinical presentation, cardiovascular involvement and disease severity. Children classified as PIMS-TS and another syndrome were more likely to require intensive care support and longer hospitalisation stay than

those with PIMS-TS only. There was a temporal and geographical association between community SARS-CoV-2 prevalence and PIMS-TS cases, both nationally and regionally, with a median lag of 16 days between COVID-19 and PIMS-TS cases in England. Latent Class Analysis (LCA) identified three different classes which broadly divided into PIMS-TS only (Class 1), PIMS-TS/KD (Class 2) and PIMS-TS/TSS (Class 3), with Class 2 cases tending to be younger, and Class 3 older.

The strong association between SARS-CoV-2 and PIMS-TS emphasises the importance of maintaining low community infection rates to reduce the risk of PIMS-TS. Understanding the relationship between SARS-CoV-2 infection and PIMS-TS could provide useful insight into the pathogenesis of both KD and TSS. Close follow-up will be important to monitor rapidly changing epidemiology as well as the short- to long-term complications in children with PIMS-TS.

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Public and patient engagement

Societi: The UK Kawasaki Disease Foundation.
Web: **https://www.societi.org.uk**

Acknowledgements

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Clinical characteristics of children with pneumococcal meningitis

Key points

- Between January 2020 and August 2021, 104 cases have been reported (69 in 2020; 33 in 2021): 51 completed, 27 excluded (Duplicates/ Error/Unable to follow up) and 26 awaited.
- Two-thirds of confirmed cases were male and half were under the age of one (50%). At least 80% had been fully vaccinated.
- The surveillance is still ongoing and due to conclude in January 2022.

Summary

Streptococcus pneumoniae is a major cause of bacterial meningitis globally, with 10% to 40% dying of their infection. Survivors of pneumococcal meningitis are more likely than any other causes of meningitis to suffer from neurological and other serious long-term complications.

The pneumococcal vaccines used in the national childhood immunisation in the UK and the Republic of Ireland (since 2006 and 2008, respectively) have been associated with a rapid decline in pneumococcal disease, including meningitis caused by the vaccine serotypes. The overall reduction, however, has been offset by a small increase in disease due to non-vaccine serotypes. Currently, nearly all pneumococcal infections in children are caused by non-vaccine pneumococcal serotypes. Because these serotypes have only emerged after the pneumococcal vaccines were introduced, we have very little knowledge of the risk, clinical severity and outcomes of pneumococcal meningitis.

Our aim is to understand the clinical severity, presenting features, acute management, clinical course and the outcomes after 12-months of such non-vaccine serotypes causing meningitis. We will compare our results with the national standard of care for children with serious infections. There are reports of extended hospitalisations for some children with pneumococcal meningitis because of prolonged inflammation after appropriate antibiotic treatment. A better understanding of the course of illness will guide clinical management, enable more accurate information to be shared with patients and their families on prognosis, and inform public health vaccine policy.

Surveillance period

January 2020 - January 2022 (inclusive).

Follow-up period: Follow-up questionnaire at 12 months after initial diagnosis, ending in January 2023.

Dr Godwin Oligbu

Methodology

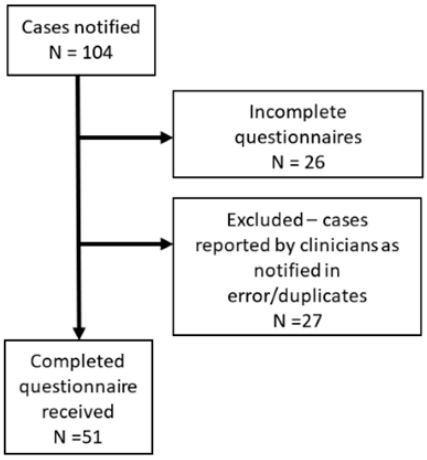
Data capture uses standard BPSU methodology. Details of the study protocol are available at **http://rcpch.ac.uk/bpsu/pneumococcal-meningitis**

Analysis

Data collection is still ongoing and analysis will be conducted at the end of the surveillance period, including the incidence. Preliminary data on some key characteristics are outlined below.

Between January 2020 and August 2021, 104 cases have been reported (69 in 2020; 33 in 2021): 51 completed, 27 excluded (Duplicates/Error/ Unable to follow up) and 26 awaited (Figure 6).

Figure 6: Cases reported between January 2020 & August 2021 in the UK and Republic of Ireland



Of the confirmed cases, most were male (29/48; 60%) and under one year of age (24/46; 52%), followed by 1-4 year olds (12/46; 26%); the rest were evenly distributed between 5-9 and 10-15 year olds. In total, 57% (28/48) of confirmed cases are either of a White ethnic background, 8% (n=4) of Mixed Ethnic groups, 6% (n=3) of Asian ethnic groups, while 27% (n=13) were unknown.

At the time of the episode, 81% (36/45) of children had been fully vaccinated against *Streptococcus pneumoniae*and 11% (5/45) partially vaccinated, leaving about 9% unvaccinated cases. One in three children were recorded to have at least one comorbidity (11/39; 28%).30-day case-fatality rate was low, with three deaths reported in this time period (6%).

Discussion

Most cases reported are in the younger age group, consistent with the general incidence of S. pneumoniae in under 16-year-olds. As expected from the high coverage for pneumococcal vaccines, most children have been fully vaccinated with pneumococcal vaccines. Serotype was rarely reported and further linkage to national datasets will be required to assess the impact of non-vaccine types. Follow up is ongoing at pace and will be completed by January 2023.

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Funding

This study has been funded by the Sir Peter Tizard Research Bursary (**http://www.rcpch.ac.uk/bpsu/bursary**) and through a grant from Action Medical Research (**https://action.org.uk**).

Public and patient engagement

Meningitis Now.

Web: **https://www.meningitisnow.org**

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The pneumococcal meningistis team would like to thank Natalie Mensah and Rashmi Malkani for their support with study administration.

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Progressive intellectual and neurological deterioration in children (including Creutzfeldt - Jakob disease)

Key points

- Continuing surveillance of UK children with progressive intellectual and neurological deterioration (PIND) is important to ensure that new cases of variant Creutzfeldt-Jakob disease (vCJD) are not being missed among the numerous rare neurodegenerative disorders of childhood.
- The study provides unique information about the epidemiology of neurodegenerative diseases in UK children. From May 1997 until 31st March 2021, 4,814 children have been notified; 2,069 children have a known diagnosis other than vCJD, with over 220 different neurodegenerative disorders in this diagnosed group.
- 139 children with suspected PIND were reported to the PIND study this year (1st April 2020 - 19th March 2021)
- Six cases of vCJD have been reported to the study since December 1998; four have been classified as "definite" and two "probable"; all have now died.

Summary

Active prospective surveillance of UK children with progressive intellectual and neurological deterioration (PIND) commenced in May 1997.[1] Funded by the National Institute for Health Research (NIHR) Policy Research Programme (PR-ST-1216-10001) it is being carried out via the BPSU in conjunction with the National Creutzfeldt-Jakob Disease Research and Surveillance Unit in Edinburgh (NCJDRSU). The study strategy is to look at the broad group of rare neurodegenerative disorders affecting children, carefully examine the clinical details and determine whether there are cases of vCJD amongst these PIND cases. This unique dataset provides the opportunity to detect vCJD cases and highlight the variety of PIND conditions in the UK.[2]

The PIND Expert Group

The main objective of this study is to provide prospective on-going surveillance for vCJD in children. This is done by identifying all diseases that meet the case definition for PIND – see below. The study provides the only means of searching for vCJD in children. In addition the study yields a UK-wide overview of childhood neurodegenerative diseases.

Methodology

Data capture uses standard BPSU methodology; details of the study protocol are available at **http://www.rcpch.ac.uk/bpsu/pind**

An Expert Group of specialists in paediatric neurology, neurogenetics and metabolic disease, plus a NCJDRSU representative, meets quarterly to review anonymised clinical information and classify cases, looking for cases of vCJD. The characteristic clinical features of vCJD have been published and provide a basis for that discussion. For instance there are characteristic features on brain MRI Scans – see Figure 7.

Surveillance period

May 1997 – April 2022 (inclusive)

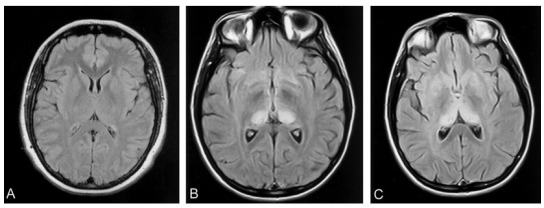
Analysis

Between May 1997 and 19th March 2021, 4,814 cases had been notified.

Definite and probable cases of vCJD: Six cases of vCJD (four definite and two probable) have been notified - the youngest was a girl aged 12 years at onset. There were three other girls (two aged 14 years and one aged 13 years at age of onset) and two boys aged 15 years at onset. The last child who developed symptoms did so in 2000. All have now died and neuropathology has confirmed vCJD in four cases; a post-mortem was not carried out on the remaining two cases.

Children with PIND who have definite diagnoses: A recent analysis showed that between May 1997 and 19th March 2021 2,155 cases meeting the PIND criteria had been notified and had been extensively

Figure 7: MRI brain scan findings in vCJD[3]



A, Normal FLAIR image at the level of the basal ganglia shows the thalamus is normally isointense or slightly hypointense relative to the putamen. This appearance is depicted with most sequences, particularly the FLAIR sequence.

B, Pulvinar sign of vCJD. FLAIR image shows marked, symmetrical hyperintensity of the pulvinar (posterior) thalamic nuclei. In this case, the pulvinar signal intensity was scored as grade 4 by both observers.

C, "Hockey-stick" sign of vCJD. FLAIR image shows symmetrical pulvinar and dorsomedial thalamic nuclear hyperintensity. This combination gives a characteristic "hockey-stick" appearance and was present in 93% of cases with FLAIR imaging.

Figure 8a: The eleven most common diagnoses in White children age <1 year.

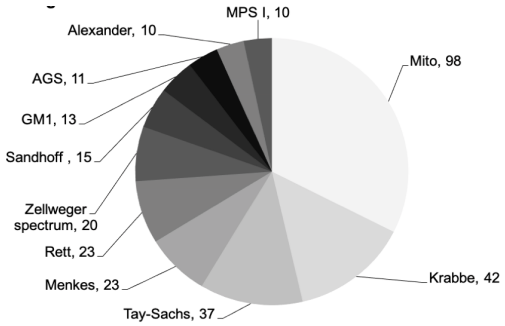
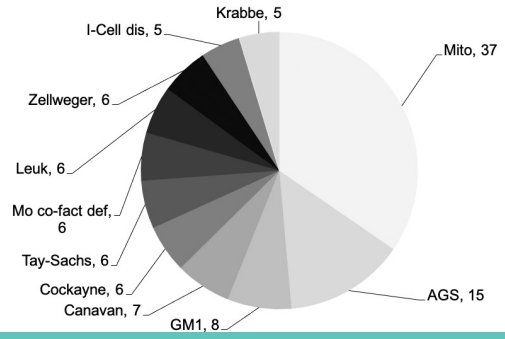


Figure 8b: The eleven most common diagnoses in Pakistani children age <1 year



Key -
AGS: Aicardi-Goutières syndrome ***GM1:*** GM1 gangliosidosis ***Mito:*** Mitochondrial disorders ***Leuk:*** Unclassified leukoencephalopathies ***MPS:*** mucopolysaccharidosis

investigated. Of these 2,069 (male 1,120, female 949) had an underlying diagnosis to explain their deterioration. The distribution by ethnic origin was: White 60%, Black 2.4 %, Indian 2%, Pakistani 18%, Bangladeshi 2%, Chinese 0.2%, Other (other ethnic groups, mixed race) 8%, Unknown 7.4%

Children with PIND and no underlying diagnosis (idiopathic group): The Expert Group has met regularly and discussed this group of children, currently 267. If a "new" variant of vCJD should arise or if the paediatric presentation differed from the adult presentation, this group could include such a case. However, there is currently no evidence of a "new" unrecognised disorder in this group.

Distribution of diseases in different age and ethnic groups: This was analysed for the period May 1997 - October 2019 and has now been published. In this period 2,255 children meeting the criteria for PIND had been notified, of whom 2,008 (male 1,085, female 923) had underlying diagnoses. There were over 220 different diseases, including six cases of vCJD. The numbers presenting in four age groups were: <1 year: 805 (40%), 1-4 years inclusive: 825 (41%), 5-9 years inclusive: 264 (13%), 10-15 years inclusive: 114 (6%). The two largest ethnic groups were White and Pakistani (58.2% and 17% of diagnosed cases). The commonest diseases in these two ethnic groups were determined for the four age groups. The distribution of diseases varied with age but there were similarities between White and Pakistani children. Figures 8a and 8b show the 11 most common diagnoses in White and Pakistani children <1 year old; 6 of the 11 commonest diagnoses in White children were among the 11 commonest diagnoses in Pakistani children.

Discussion

The National Creutzfeldt-Jakob Disease Research and Surveillance Unit in Edinburgh reports that , as of 1st March 2021 there have been 178 deaths from definite or probable vCJD in UK patients of all ages. Until 2016 all these cases were methionine homozygous (MM) at codon 129 of the prion protein gene (PRNP). The first and only confirmed methionine/valine (MV) heterozygous vCJD adult case was identified four years ago (2016).[4] There remains concern that more childhood cases may appear, perhaps with the MV genotype. Children are still at risk of vCJD infection by blood, plasma products, surgical and dental instruments and theoretically via vertical transmission.

Continued surveillance for vCJD is essential and the PIND Study continues to yield unique information about the epidemiology of childhood neurodegenerative disorders in the UK.

Acknowledgements

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3. Collie DA, Summers DM, Sellar RY et al. Diagnosing Variant Creutzfeldt-Jakob Disease with the Pulvinar Sign: MR Imaging Findings in 86 Neuropathologically Confirmed Cases. Am J Neuroradiol 2003;24:1560–1569.

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Funding

National Institute for Health Research Policy Research Programme [PR-ST-1216-10001].

Public and patient engagement

Creutzfeldt-Jakob Disease Support Network.
Web: **http://www.cjdsupport.net**

Batten Disease Family Association.
Web: **http://www.bdfa-uk.org.uk**

Society for Mucopolysaccharide Diseases.
Web: **http://www.mpsociety.co.uk**

Alex TLC (Adrenoleukodystrophy).
Web: **http://www.alextlc.org**

The Cure & Action for Tay-Sachs (CATS) Foundation.
Web: **http://www.cats-foundation.org**

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Sydenham's chorea

Key points

- Over 24-months, 72 reports were made via BPSU, of which 43 met the surveillance definition of being cases of suspected or confirmed SC (12 susspected, 31 confirmed).
- We are in the process of finalising the numbers and incidence estimates, as well as completing descriptive analysis of the cases.
- Follow-up is also in progress: cases are being followed up over a 24-month period ending in December 2022 to examine the course and outcomes of SC.

Summary

Sydenham's chorea (SC) is a rare condition which can affect the brain following infection with a type of bacteria (Streptococcus). It largely affects children and young people. Symptoms include abnormal body movements and muscle weakness, which range from mild to severe and may disrupt a child's ability to carry out activities of daily living like writing and walking. Whilst SC may get better within six months, symptoms can return repeatedly over the course of two years or longer. SC is often accompanied by emotional and behavioural symptoms such as hyperactivity, obsessions and compulsions, and anxiety. In the UK and the Republic of Ireland (ROI), SC is currently considered a 'rare disease'; but little is known about how many children are affected by the disorder, what happens to them after diagnosis, or about their needs.

Through this research we are studying the numbers, characteristics, management and outcomes of new cases of SC aged between 0 and 16 years in the UK and ROI. Information on investigations, management, recovery and outcomes such as educational difficulties occurring as a result of SC is being sought. As well as describing the current pattern of SC, it is hoped findings will raise awareness amongst clinicians to improve diagnosis, contribute to planning effective services, and assist in designing research trials to test treatments.

Surveillance period

November 2018 - December 2020 (inclusive).

Follow-up period: Until December 2022 at 12-months and 24-months.

Methodology

Data capture uses standard BPSU methodology; details of the study protocol are available at **http://www.rcpch.ac.uk/bpsu/sydenhams**

A parallel Child and Adolescent Psychiatry Surveillance System (CAPSS) study is running from May 2019 to December 2020. Data collection will focus on the psychiatric presentation and the course of those associated symptoms. Analysis will therefore be conducted separately for each study. However, we will also conduct analysis on the crossover between cases reported by paediatricians and by child psychiatrists; and compare characteristics between these two groups.

Dr Tamsin Newlove-Delgado

Analysis

Surveillance has finished but data analysis and incidence estimates have yet to be completed. Provisional findings are presented here. Cases meeting surveillance case definition of suspected or confirmed SC, will be finally confirmed after the 12-month follow-up. Over 24 months, 72 reports were made via BPSU, of which 43 met the surveillance case definition of being eligible cases of suspected or confirmed SC (12 suspected, 31 confirmed). The remainder being ineligible (*n*=8) or duplicates (*n*=6), or unable to follow up (*n*=15) (Figure 9).

Preliminary analysis of the characteristics of 23 cases which met the surveillance definition from the first 12-months of surveillance are as follows. The mean age of presenting cases was 9 years old, ranging from four years to 15 years of age, and 60% were female. Most (65%) presented with 'moderate' severity of chorea. After chorea, the most common neurological features reported were loss of fine motor skills, gait disturbance, and dysarthria (Figure 10, overleaf). Over 75% also presented with emotional and/or behavioural symptoms. Of the

Figure 9: Breakdown of case reports November 2018-November 2020

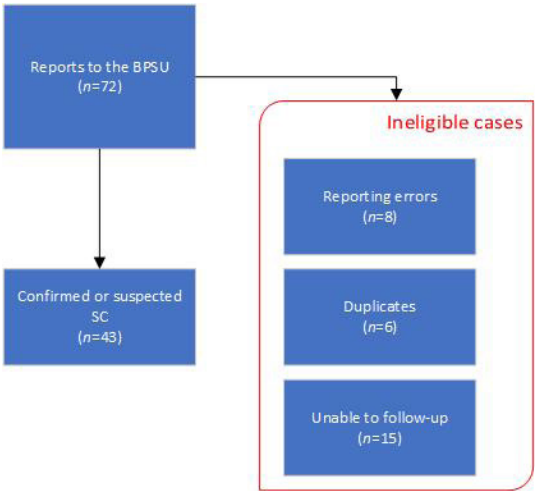
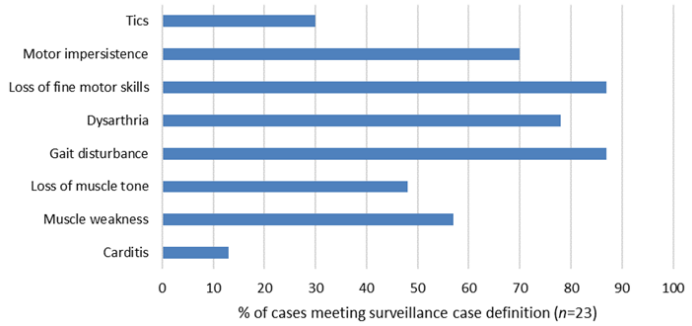


Figure 10: Presenting neurological features



23 cases meeting the surveillance definiton: 73% presented with emotional lability, 47% anxiety, and 43% inattention or attention deficit. Almost all cases had evidence of prior streptococcal infection, and were prescribed courses of antibiotics of varying duration, some had symptomatic treatment, for example with anticonvulsants and neuroleptics. 22% received immunomodulatory treatment with steroids or immunoglobulins.

Discussion

Whilst SC remains a rare condition, our findings confirm that paediatricians should remain vigilant to its presenting features. The analysis of the first 12 months' data characterise some of the most common presenting features, and also highlight that emotional and/or behavioural symptoms were common in the cases reported by paediatricians. Almost 80% had emotional lability on presentation, and symptoms of anxiety and/or inattention/attention deficit were also reported in approximately a third of cases. However, despite this presentation, no reports were made by child and adolescent psychiatrists in our parallel surveillance study through CAPSS; which is an interesting finding. Explanations are being sought for this, but one reason may be that children with these symptoms are being seen by psychologists within paediatric services, rather than CAMHS. Clinical management appears variable, suggesting a role in exploring 'best practice' through consensus development and further research. We expect to provide a fuller breakdown of clinical management in our final analysis. In the next phase of this study we will follow-up cases with their clinicians at 12 months and 24 months post-notification, to study the course and clinical outcomes of the condition. This will allow us to provide fuller information for families; we have been working with the Sydenham's Chorea Association and will be providing information for their website as well as presenting at their events.

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Public patient engagement

The Sydenham's Chorea Association
Web: **http://www.sydenhamschorea.org.uk**

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Appendix - Publications 2020 - 2021

Behçet's Syndrome

1. Pain CE, Beresford MW, Fortune F, Lai ET, Murphy R, Taylor-Robinson D, Brogan PA, Moots RJ. Behçet's syndrome in children and young people in the United Kingdom and the Republic of Ireland: a prospective epidemiological study. Rheumatology. 2021 Feb 2.

BPSU

2. Lynn RM, Avis JL, Lenton S, Amin-Chowdhury Z, Ladhani SN. Delayed access to care and late presentations in children during the COVID-19 pandemic: a snapshot survey of 4075 paediatricians in the UK and Ireland. Archives of disease in childhood. 2021 Feb 1;106(2):e8-.

Bronchopulmonary dysplasia

3. Naples R, Ramaiah S, Rankin J, Berrington J, Harigopal S. Life-threatening bronchopulmonary dysplasia: a British Paediatric Surveillance Unit Study. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2021 Jun 27.

Death in epilepsy

4. Abdel-Mannan O, Sutcliffe AG. A national surveillance study of childhood epilepsy mortality in the UK and Ireland. European journal of neurology. 2020 Feb;27(2):327-33

Female genital mutilation

5. Hodes D, Ayadi O'Donnell N, Pall K, Leoni M , Lok W, Debelle G, Armitage A, Creighton SM Lynn RM. Female Genital Mutilation in children and young people under 16 years of age; results of an epidemiological surveillance study. ADC in press 2020

Food protein-induced enterocolitis syndrome

6. Stiefel G, Alviani C, Afzal NA, Byrne A, du Toit G, DunnGalvin A, Hourihane J, Jay N, Michaelis LJ, Erlewyn-Lajeunesse M. Food protein-induced enterocolitis syndrome in the British Isles. Archives of Disease in Childhood. 2021 Aug 26.

Invasive listeria infection

7. Vergnano S, Godbole G, Simbo A, Smith-Palmer A, Cormican M, Anthony M, Heath PT. Listeria infection in young infants: results from a national surveillance study in the UK and Ireland. Archives of Disease in Childhood. 2021 May 12.

Multisystem inflammatory syndrome, Kawasaki disease and toxic shock syndrome

8. Flood J, Shingleton J, Bennett E, Walker B, Amin-Chowdhury Z, Oligbu G, Avis J, Lynn RM, Davis P, Bharucha T, Pain CE. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS): Prospective, national surveillance, United Kingdom and Ireland, 2020. The Lancet Regional Health-Europe. 2021 Apr 1;3:100075.

Neonatal complications of coronavirus disease (COVID-19)

9. Gale C, Knight M, Ladhani S, Draper ES, Sharkey D, Doherty C, Mactier H, Kurinczuk JJ; Members of Neonatal Complications of COVID-19 Surveillance Group. National active surveillance to understand and inform neonatal care in COVID-19. Arch Dis Child Fetal Neonatal Ed. 2020 Jul;105(4):346-347. doi: 10.1136/archdischild-2020-319372. Epub 2020 Jun 14.

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Neonatal HSV

12. Tookey PA, Mahdavi S, Peckham CS. Surveillance of neonatal herpes in the British Isles 2004-2006. F1000Research. 2020 Mar 4;9(163):163.

Patent ductus arteriosus in pre-term infants

13. Warnock A, Szatkowski L, Lakshmanan A, Lee L, Kelsall W. Surgical management of patent ductus arteriosus in pre-term infants-a british paediatric surveillance study. BMC pediatrics. 2021 Dec;21(1):1-8.

Progressive intellectual and neurological deterioration

14. Verity C, Baker E, Maunder P, Pal S, Winstone AM. Differential diagnosis of progressive intellectual and neurological deterioration in children. Developmental Medicine & Child Neurology. 2021 Mar;63(3):287-94.

Visual impairment and blindness

15. Teoh LJ, Solebo AL, Rahi JS, Morton C, Allen L, McPhee D, Brennan R, Pennefather P, Kattakayan C, Ramm L, Abbott J. Visual impairment, severe visual impairment, and blindness in children in Britain (BCVIS2): a national observational study. The Lancet Child & Adolescent Health. 2021 Mar 1;5(3):190-200.

Membership of Scientific Committee 2020

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